Update in Diabetes Management – Insulin Therapies

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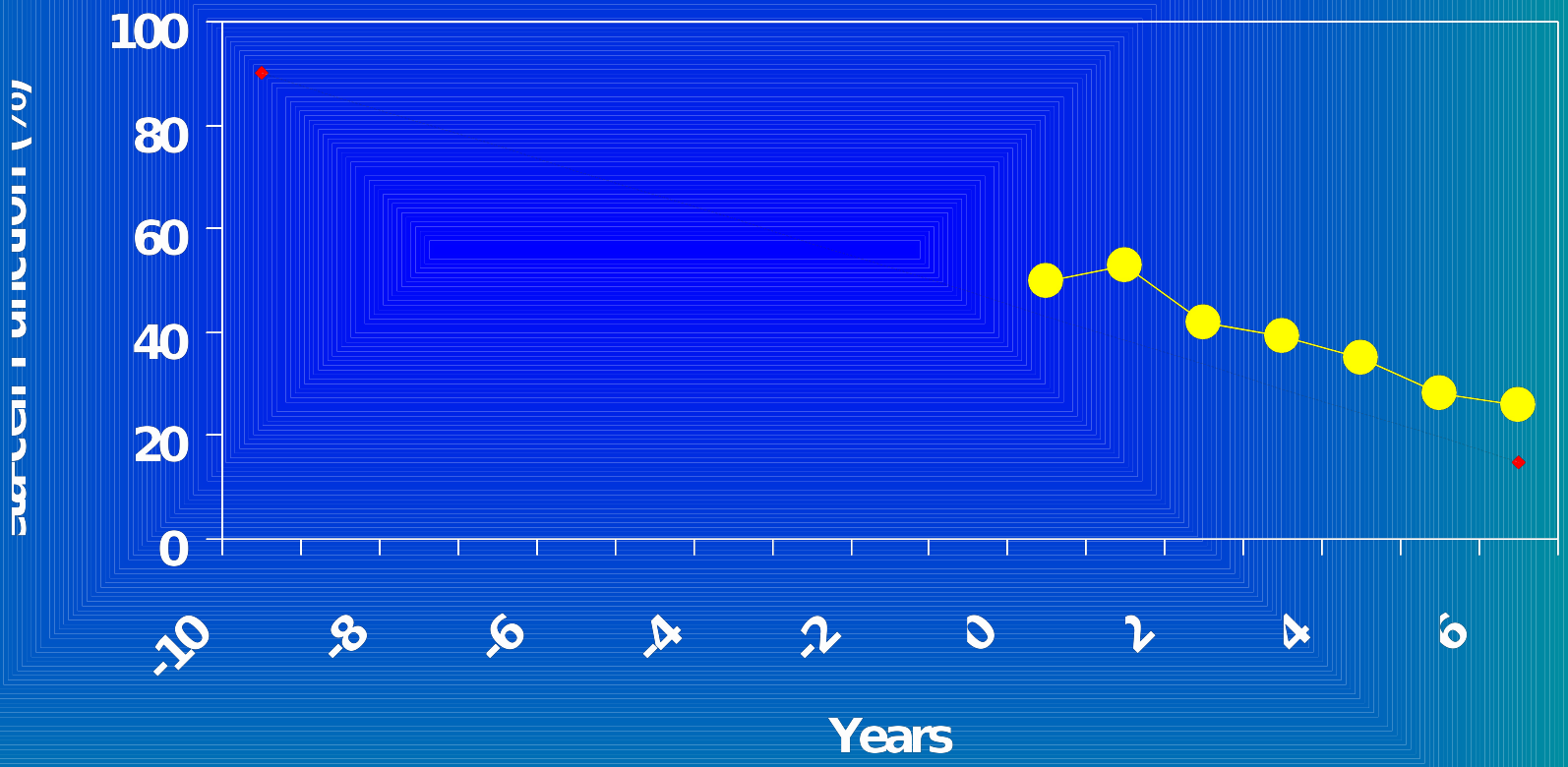
Rationale for Insulin Therapy in Type 2 DM

- Up to 1/3 of patients may require insulin to achieve adequate glycemic control
- The UKPDS Trial
  - Demonstrated progressive hyperglycemia
  - Decrease in β-cell function
  - All treatment groups

Gerich JE. Am J Med 2002;113:308-316.

Beta-cell decline



Mudaliar S, et al. Endo and Metab Clin of NA 2001;03(4):935-982.

Indications for Insulin Therapy in Type 2 DM

- Persistently elevated FPG ≥ 300 mg/dL and ketonuria or ketonemia
- Persistent elevations of FPG ≥ 300 mg/dL and sx of polyuria, polydipsia, and weight loss
- All women with gestational diabetes whose disease is not controlled with diet alone and women with Type 2 DM who become pregnant

Insulin Preparations

- Lispro/Aspart/Glulisine
  - Humalog ®, NovoLog®, Apidra®
- Human Regular
  - Humulin R ®, Novolin R ®
- Human NPH/Lente
  - Humulin N®, Novolin N®
  - Humulin L ®, Novolin L ®
- Ultralente
  - Humulin U ®
- Glargine
  - Lantus®

Activity Profiles

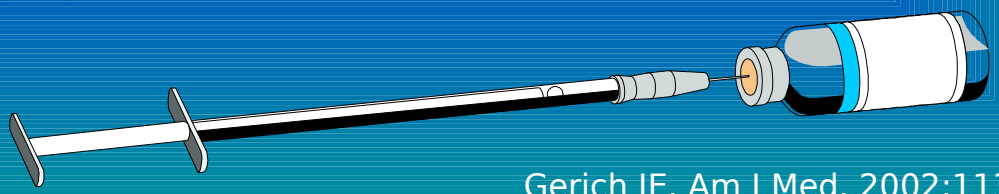
Preparation	Onset	Peak	Duration
Rapid-acting			
Insulin lipsro	15 minutes	30-60 minutes	3 hours
Insulin aspart	15 minutes	30-60 minutes	3 hours
Short-acting			
Regular insulin	30 minutes	2-5 hours	5-8 hours
Intermediate-acting			
Isophane (NPH) insulin	1-2 hours	6-10 hours	16-20 hours
Insulin zinc (Lente)	1-2 hours	6-12 hours	18-24 hours
Long-acting			
Insulin zinc (Ultralente)	4-6 hours	10-18 hours	24-48 hours
Insulin glargine	2 hours	None	>24 hours
Mixtures			
Isophane/regular insulin 70/30, 50/50	45 minutes	7-12 hours	16-24 hours
NPL/lispro Mix 75/25	5 minutes	7-12 hours	1-24 hours

NPH = neutral protamine Hagedorn; NPL = neutral protamine lispro

Campbell RK, et al. *J Am Pharm Assoc* 2002;42:602-

Novel Insulins

- Novel Bolus Insulins
  - Insulin lispro
  - Insulin aspart
  - Inhaled insulin
- Novel Basal Insulins
  - Insulin glargine
  - Fatty acid acylated insulins
    - Insulin detemir



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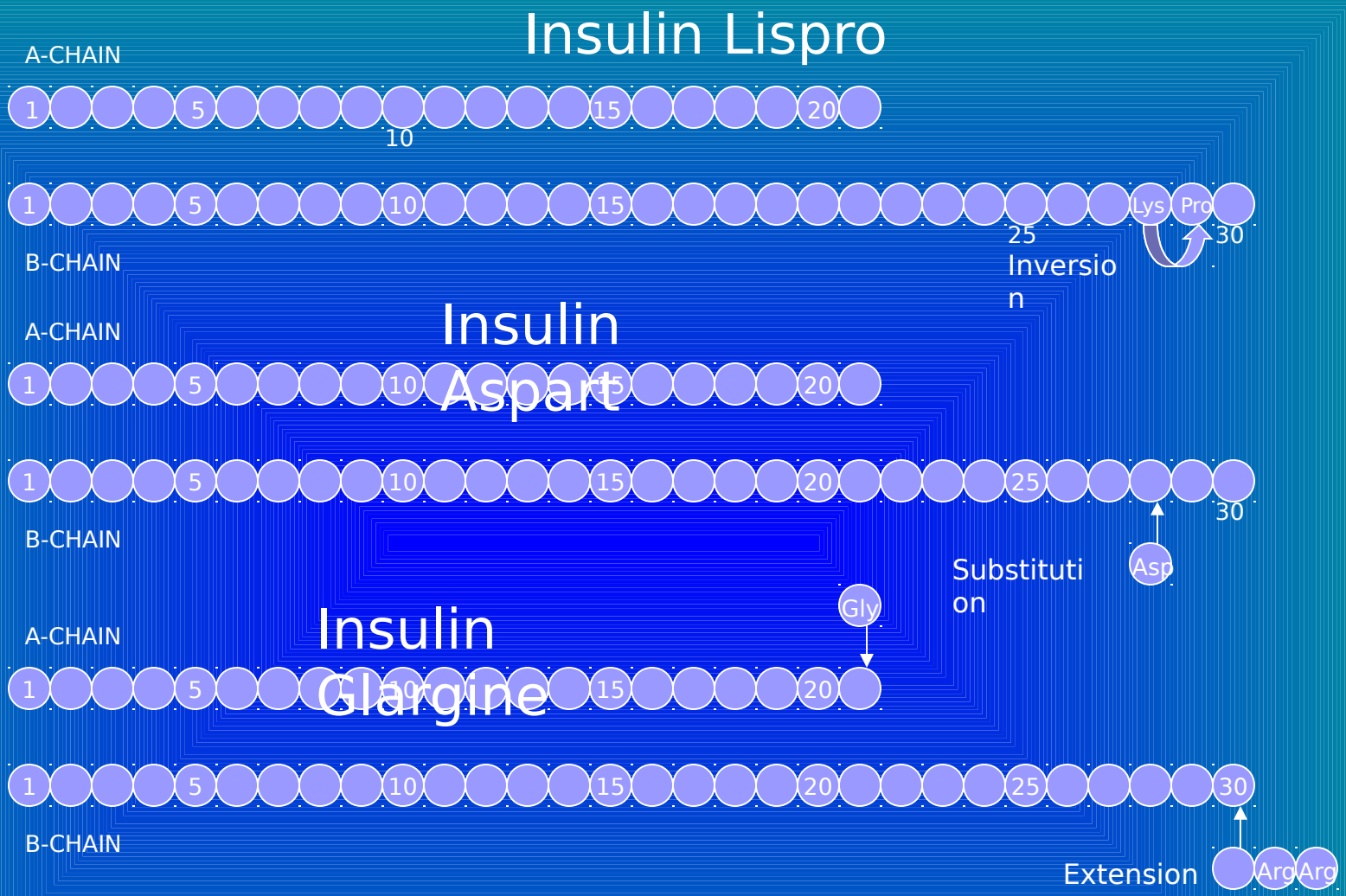
Insulin Lispro
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Insulin Lispro (Humalog®)

- Advantages
  - Improved glycemic control in patients with Type 1 DM who inject insulin immediately before meals
  - Subcutaneous absorption characteristics and plasma profile more closely resembling meal-stimulated physiologic insulin release
  - More flexible lifestyle from immediate preprandial dosing schedule
  - Rapid-acting insulin
  - Ability to administer a few minutes before meals

Insulin Aspart (NovoLog®)

- Advantages
  - Absorption more than twice as fast, peak levels more than twice as high, as with regular insulin
  - Improved glycemic control in patients with Type 1 DM injecting insulin immediately before meals (in conjunction with regular basal insulin)

Insulin Lispro/Aspart

- Disadvantages
  - More rapid onset of ketoacidosis in cases of continuous subcutaneous insulin infusion pump failure
  - Unknown teratogenicity and long-term safety profile
  - Higher cost
  - Need for one to two more daily insulin injections

Insulin Glargine (Lantus®)

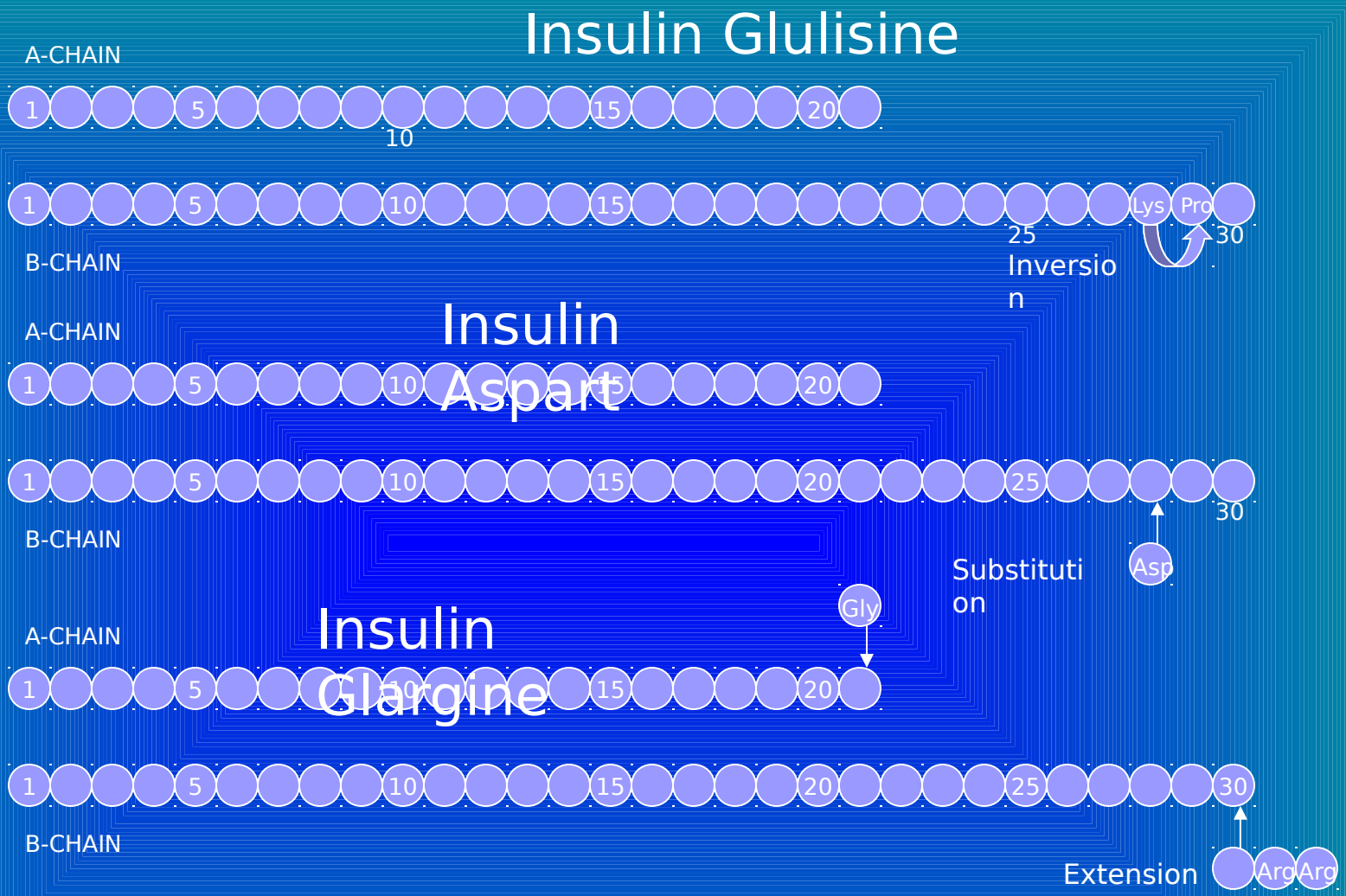
- Long-acting, “peakless” insulin
- Administered once daily
- Lower risk of nocturnal hypoglycemia
- Less weight gain compared with NPH
- Often used in combination with other insulins, oral agents, or possibly inhaled insulin

Newer Therapies

- Insulin glulisine (Apidra®)
- Insulin detemir (Levemir®)
- Inhaled insulin (Exubera®)
- Pramilintide acetate (Symlin®)
- Exenatide (Byetta®)
- Sitagliptin (Januvia®)

Insulin glulisine (Apidra®)

- Class: Rapid-acting insulin
- Indication
  - Bolus insulin designed for meal-time coverage of blood sugars in Type 1 or 2 DM
- Administration
  - Injected subcutaneously 15 minutes before or after a meal
- Adverse effects
  - Hypoglycemia, injection site reactions, lipodystrophy, pruritis, rash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Insulin Glargine
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Insulin detemir (Levemir®)

- Class: Long-acting insulin
- Indication
  - Basal insulin designed for meal-time coverage of blood sugars in Type 1 or 2 DM
- Administration
  - Injected SQ once or twice daily every evening or hs
  - Should not be mixed with other insulins

Insulin detemir (Levemir®)

- Dose
  - Start with a 1:1 ratio from a basal insulin
  - Can be given q12 hours
  - Some pts may need higher doses of Levemir than NPH
  - Insulin naïve pts with poor control on PO drugs: 0.1-0.2 units/kg once daily in evening or 10 units once/twice daily
- Adverse effects
  - Hypoglycemia, injection site reactions, lipodystrophy, pruritis, rash

Insulin detemir (Levemir®)

- Advantage
  - Less burning on injection
  - Cheaper than Lantus®

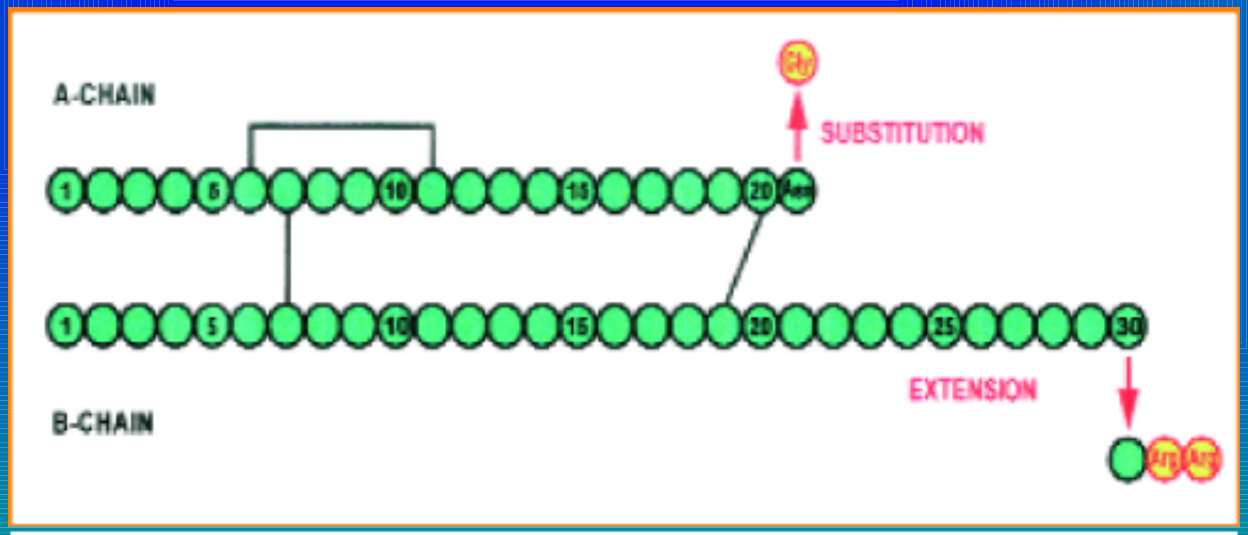


Fig. 3. Structure de l'insuline glargine.

Inhaled Insulin (Exubera™)

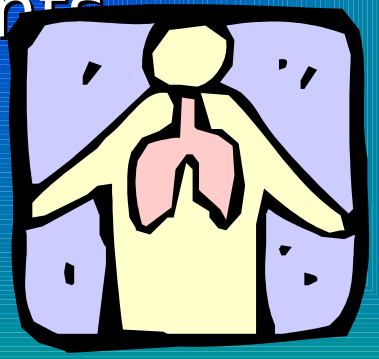
- Insulin human [rDNA origin] inhalation powder
- Rapid-acting, dry-powder insulin
- Should be given within 10 minutes before a meal
- Side Effects: hypoglycemia, cough, dry mouth, chest discomfort
- Not recommended for those with a chronic lung disease (asthma, COI

Inhaled Insulin (Exubera™)

- Advantages
  - Reaches peak level more than twice as fast as insulin delivered via subcutaneous injections
  - Offers more flexible lifestyle through immediate pre-meal administration
  - Resembles meal-stimulated physiologic insulin release more closely
  - Reduces duration of postprandial increases in blood glucose levels
  - May be linked to less weight gain
  - Eliminates need for preprandial injections

Inhaled Insulin (Exubera™)

- Disadvantages
  - Requires much higher insulin doses because of limited penetration to the alveoli
  - Higher cost
  - Permits less precise dose calibration because of 1-mg and 3-mg minimum dose increments



Pramlintide (Symlin®)

- Class: Amylin agonists
- Indication: Patients with Type 1 or 2 DM uncontrolled on QID insulin therapy
- MOA
  - Synthetic analog of human amylin
  - Naturally occurring hormone made in pancreatic beta cells
  - Reduction of postprandial glucagon secretion
  - Regulation of gastric emptying, and therefore the rate of nutrient delivery (exogenous glucose) to the small intestine

Pramlintide (Symlin®)

- Administration
  - Given SQ 15 minutes prior to meals
  - Do not mix with other insulins
  - Patient must give multiple injections at separate times
- Caution: Initially decrease insulin doses by 50% to avoid hypoglycemia
- Medication Error Risk!!
  - Doses available in 15, 30, 60, and 90mcg doses
  - Patient must draw up dose in unit syringes

Cost Comparison

Drug	Vial	Cost
Apidra®	10ml	$45.39
Humalog®	10ml	$46.33
Novolog®	10ml	$25.19
Humulin® R	10ml	$11.33
Humulin® N	10ml	$11.33
Exubera™ Kit	Starter kit	$109.17
Exubera™	Pack - #270	$101.86
Byetta™	250mcg/ml	$108.78

The Incretin System

- Incretin hormones
  - Glucose-dependent insulinotropic polypeptide (GIP)
  - Glucagon-like peptide-1 (GLP-1)
- Eating causes secretion of hormones from the GI tract
- Enzyme
  - Dipeptidyl peptidase-4 (DPP-4) inactivates GLP-1
- G-protein-coupled receptors (GPCR's)

Lancet 2006;368:1696-705.

The Incretin System

- Actions of GLP-1
  - Inhibits glucagon secretion
  - Inhibits gastric emptying
  - Inhibits food ingestion
  - Promotes glucose disposal
  - GLP-1 receptors (GLP-1R) are expressed in islet α and β cells and in peripheral tissues

Lancet 2006;368:1696-705.

Exenatide (Byetta™)

- Class
  - Incretin mimetics
  - GLP-1R agonists
- Indication
  - Adjunctive therapy in patients with Type 2 diabetes uncontrolled on metformin, a sulfonylurea, or their combination
- Do not need to be on insulin therapy

Exenatide (Byetta™)

- MOA
  - Mimics the effects of the incretin glucagon-like peptide 1 (GLP-1)
  - Enhances glucose-dependent insulin secretion by pancreatic beta-cells
  - Suppresses inappropriately elevated glucagon secretion
  - Slows gastric emptying
- Administration
  - SQ injections in pre-filled pens
- Major adverse effect: nausea

Sitagliptin (Januvia®)

- Class
  - Dipeptidyl peptidase-4 inhibitor (DPP-4)
- Indication
  - Treatment of DM2
  - Monotherapy and as add-on therapy to metformin or thiazolidinediones (TZDs)
  - NOT approved with insulin or sulfonylureas
- Dose: 100 mg once daily

Sitagliptin (Januvia®)

- MOA
  - Enhances the incretin system by inhibiting DPP-4, which breaks down GLP-1
  - Helps to regulate glucose by affecting beta cells and alpha cells
- Adverse effects
  - (≥ 5%) stuffy or runny nose, sore throat, URI, and headache

Sitagliptin (Januvia®)

- Advantages
  - Does not cause weight gain
  - Less GI side effects
- Safety concerns
  - May effect other endogenous hormones
  - No long-term studies published
  - 52 week ongoing study of patients inadequately controlled on metformin monotherapy
    - Pts randomized to either sitagliptin 100mg qd plus metformin or glipizide plus metformin
    - Abstract suggested only HbA1c %0.67 decrease

Diabetes Care 2006. 29(12):2632-

On the Horizon

- GLP-1R Agonists
  - Liraglutide – Novo Nordisk
- DPP-4 inhibitors
  - Vildagliptin (Galvus®) – Novartis
  - Saxagliptin
  - Denagliptin

Lancet 2006;368:1696-705.

Summary

- Diabetes affects a major percentage of the US population
- Screening of at-risk patients early on is essential to delay or prevent DM from developing
- Treat the whole patient, not just their DM
- More options on the horizon for controlling blood sugars, but be wary